



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Dear Dr.

To obtain needed pediatric information on hydroxyurea, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the trial in pediatric patients described below. This study investigates the potential use of hydroxyurea in the treatment of children with sickle cell disease.

Please submit information from the following type of study:

- ***Type of study:***

Open label pharmacokinetic and safety study in patients from 2 to 5 years of age.

- ***Indication to be studied:***

Sickle cell disease

- ***Age group in which study will be performed:***

Patients from 2 to 5 years of age

- ***Study:***

The study should be conducted in at least 6 sickle cell patients who have or who are expected to develop, renal compromise. The study should evaluate relevant indicators of organ function such as CBC, serum creatinine, and liver function tests in addition to the pharmacokinetic parameters

described below. The data should be analyzed using appropriate pharmacokinetic methods (e.g., traditional, population) to estimate the pharmacokinetic parameters which will include AUC, C_{max} , T_{max} , CL/F , V_{ss}/F and $T_{1/2}$. For a population pharmacokinetic study, at least four blood samples should be obtained from each of the patients. Blood samples should be collected using an optimal sampling scheme. Fixed sampling times should be avoided. An analysis of the effect of demographic covariates (e.g., age, gender, and body weight) on pharmacokinetic parameters should be assessed. If possible, first and repeat dose data should be included in the pharmacokinetic analysis.

- ***Drug information:***

Dosage form: Age appropriate formulation
Route of administration: Oral
Regimen: To be determined by study results

Full study reports of any relative bioavailability studies should be submitted to the Agency.

- ***Drug specific safety concerns:***

Myelosuppression, thrombocytopenia, long term follow-up effects (such as secondary malignancies and effects on growth and development)

- ***Statistical information, including power of study and statistical assessments:***

The study may be submitted with descriptive statistics and the numbers and types of clinical events along with the pharmacokinetic parameters described below. The study should have at least 16 evaluable patients adequately distributed across the age group.

- ***Labeling that may result from the study:***

Appropriate sections of the label may be changed to incorporate the findings of the study.

- ***Format of reports to be submitted:***

Full study reports and published studies not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study must be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the following designations must be used: Hispanic/Latino or Not Hispanic/Latino.

- ***Timeframe for submitting reports of the study:***

Reports of the above studies must be submitted to the Agency on or before June 1, 2006. Please keep in mind that pediatric exclusivity attaches to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

- *Response to Written Request:*

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the appropriate studies to your investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a new drug application (NDA) or as a supplement to an approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if changes to this Written Request are agreed to by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, contact Christy Cottrell, Consumer Safety Officer, at (301) 594-5761.

Sincerely,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Robert Temple
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